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(71) Applicant: REPLIGEN CORPORATION [US/US]; 117 Fourth Avenue, Needham, MA 02194 (US).

(72) Inventors: BECK, Victoria; 11 McIntosh Lane, Bedford, NH 03110 (US). RIMLAND, Bernard; 4758 Edgeware Road, San Diego, CA 92116 (US).

(74) Agent: FASSE, J., Peter; Fish & Richardson, P.C., 225 Franklin Street, Boston, MA 02110–2804 (US).

(54) Title: USE OF SECRETIN FOR THE TREATMENT OF AUTISM AND OTHER NEUROLOGICAL, BEHAVIORAL AND IMMUNOLOGICAL DISORDERS

(57) Abstract

Secretin and secretin compositions are used for the treatment of neurological, behavioral, and immunological disorders. The methods include administering an effective amount of secretin to a patient. Various methods and compositions for administering an effective amount of secretin can be used.

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USE OF SECRETIN FOR THE TREATMENT OF AUTISM AND OTHER NEUROLOGICAL, BEHAVIORAL AND IMMUNOLOGICAL DISORDERS

Background of the Invention

Autism is a disabling neurological disorder that affects thousands of Americans and encompasses a number of subtypes, with various putative causes and few documented ameliorative treatments. The disorders of the autistic spectrum may be present at birth, or may have later onset, for example, at ages two or three. There are no clear cut biological markers for autism. Diagnosis of the disorder is made by considering the degree to which the child matches the behavioral syndrome, which is characterized by poor communicative abilities, peculiarities in social and cognitive capacities, and maladaptive behavioral patterns.

A number of different treatments for autism have been developed. Many of the treatments, however, address the symptoms of the disease, rather than the causes. For example, therapies ranging from psychoanalysis to psychopharmacology have been employed in the treatment of autism. Although some clinical symptoms may be lessened by these treatments, modest improvement, at best, has been demonstrated in a minor fraction of the cases. Only a small percentage of autistic persons become able to function as self-sufficient adults.

Although much controversy exists about the causes and treatments of autism, a few established biomedical findings have been made. Many individuals with autism experience intestinal difficulties, often including the inability to digest gluten and casein. Abnormalities have also been found in the metabolism of the neurotransmitter serotonin and in various parameters of

immune system functions, for example, elevated Measles, Mumps and Rubella (MMR) titers. Prior to the discovery of the present invention, however, no useful links had been made between these biomedical findings, nor had any successful treatments been derived therefrom, as disclosed in various articles incorporated herein by reference. Priven, J. (1997), "The biological basis of autism." Current Opinion in Neurobiology, 7, 708-712; Rapin, L. & Katzman, R. (1998), "Neurobiology of autism," Ann. Neurology, 43, 7-14; Wing, L. (1997), "The autistic spectrum," The Lancet, 350, (Dec. 13), 1761-1765.

Similar to autistic spectrum disorder, many other behavioral, neurological and immunological disorders have been equally difficult to understand and to effectively treat. Such disorders include depression, obsessive-compulsive disorder, Alzheimers, allergies, anorexia, schizophrenia, as well as other neurological conditions resulting from improper modulation of neurotransmitter levels or improper modulation of immune system functions, as well as behavioral disorders such as ADD (Attention Deficit Disorder) and ADHD (Attention Deficit Hyperactivity Disorder), for example.

Accordingly, a need exists for a method and composition for the treatment of autism and other behavioral, neurological and/or immunological disorders.

The hormone secretin is a polypeptide hormone secreted by the mucosa of the duodenum and upper jejunum when acid chyme enters the intestine. The hormone secretin stimulates the pancreatic acinar cells to release bicarbonate and water, which are excreted into the duodenum and change the pH in the gut from acid to alkaline, thereby facilitating the action of digestive enzymes. Secretin is always used and indeed is intended only to be used in diagnostic tests given to patients

with gastrointestinal disorders to stimulate the release of pancreatic juices for testing purposes.

Summary of the Invention

The present invention features methods and compositions for the treatment of neurological, immunological, and other disorders in a patient. The methods include the step of stimulating the secretion of pancreatic juices in the patient. In one embodiment, stimulating the secretion of pancreatic juices comprises the step of administering to the patient an effective amount of natural or synthetic secretin. One method of the present invention is for the treatment of autistic spectrum disorder.

According to one method of administering secretin, the secretin is administered by infusion and the effective amount is generally 2 clinical units (CU) per kilogram (kg) of body weight given intravenously within 1 minute. In another method, the secretin is administered transdermally by applying a transdermal carrier substance, such as dimethyl sulfoxide (DMSO) to the skin, applying crystalline secretin in an effective amount onto the carrier substance, and rubbing the composition into the skin. One example of an effective amount of secretin administered transdermally includes about 15 CU of crystalline secretin.

Other methods of administering secretin include, but are not limited to, administering secretin transdermally with a gel (e.g., a Pluronic-Lecithin-Organogel (PLO) gel), lotion or patch; administering secretin with a suppository; administrating secretin orally, as tablet, capsule or lozenge; administrating secretin by inhalation (e.g., as an aerosol) either through the mouth or the nose; administering secretin intranasally (e.g., as a snuff); and administering

secretin using acoustic waves to permeate the skin. The present invention also contemplates other physiologically acceptable carriers or excipients for carrying an effective amount of secretin into the patients body.

In another embodiment, the method for stimulating the secretion of pancreatic juices comprises the step of causing the body to secrete secretin in an effective amount to at least ameliorate and preferably treat autism and other neurological and/or immunological disorders. This method includes, for example, stimulating or otherwise causing the duodenum and upper jejunum to secrete the hormone secretin for one or more of the purposes described herein.

The present invention also features compositions for use according to the above methods. In one embodiment, a pharmaceutical composition, according to the present invention includes an effective amount of secretin together with a suitable volume of sodium chloride for dissolving the secretin and carrying the secretin into the body by infusion. In another embodiment, a composition according to the present invention includes an effective amount of secretin and a transdermal carrier substance, such as DMSO or PLO gel for carrying the secretin into the body transdermally. Other compositions include an effective amount of secretin together with physiologically acceptable carriers or excipients for carrying the secretin into the patients body. The present invention contemplates the use of both natural and synthetically produced secretin.

Description of the Preferred Embodiments

The present invention will be better understood from the following examples which are given by way of illustration and not by way of limitation. The patient, the same in both examples, is a boy with symptoms of

autism. Although only two examples of treatment are presented on the same patient, the present invention has been tried on a number of children in accordance with the method of the first example with similar satisfactory results.

The patient in the present examples developed normally until about fourteen months of age, with the exception of gastrointestinal problems (i.e., chronic diarrhea and constipation) which began at about six months. At about thirteen months, when whole milk was introduced into his diet, the patient began having reoccurring ear infections. At about fourteen months, the patient appeared to lose the ability to process language, first receptively (at about 14 months) then expressively (at about 16 months). The patient also experienced episodes of shivers that appeared to be intermittent seizures.

After consulting with numerous neurologists, pediatricians, child development specialists, audiologists, endocrinologists, allergists, and other medical professionals, no consistent diagnosis had been reached. Although not clinically diagnosed with autism, the patient exhibits a number of behavioral symptoms of autism and pervasive developmental disorder (PDD) in general. The term autism is used herein for reference purposes only, and this invention is intended to apply to any number of pervasive developmental disorders as well as neurological and immunological disorders.

Prior to receiving the treatment with secretin, a single photon emission computed tomography (SPECT) scan of the brain revealed a decreased perfusion in the right hemisphere and left temporal lobe, with the most severe decrease in the right parietal occipital region. Also, steady state auditory evoked responses recorded in response to rapid amplitude and frequency modulations of

a 1 kHz tone were abnormal, suggesting disturbances of neural mechanisms responsible for frequency and amplitude modulation analysis. Further, the patients secretin cells prior to receiving treatment, measured at a level of 9, are far below the normal limit in the range of 20-70.

EXAMPLE 1

When the patient was three years old, the secretin was administered by way of an infusion as part of an upper gastrointestinal endoscopy. The secretin was used in this diagnostic procedure at the request of the patients parents, one of which is an inventor of the present invention. The secretin used in this procedure is known as Secretin-Ferring available from Ferring Laboratories, Inc., Suffern, New York (See Appendix A). The secretin was dissolved in a 7.5 solution of sodium chloride and administered in a dosage of 2 clinical units (CU) per kilogram (kg) body weight by intravenous injection over one minute. (I.E. 30 IU IV for approximately 15 kilograms of body weight.)

Immediately after the administration of the secretin, the diagnostic testing revealed that the patients pancreas responded, quite surprisingly, with an unusually large amount of pancreatic juice being released (approximately 10 ml/min compared to a usual rate of 1-2 ml/min). The diagnostic tests performed on the patient during this procedure also indicated gastric inflammation. Within days after the administration of secretin, the patients chronic abnormal bowel movements became normal, although no changes had been made in the patients diet. Within weeks after the treatment, the patient was able to make normal eye contact, language appeared for the first time in two years, and other behavioral and developmental problems improved

remarkably. The following Table I summarizes the improvements observed in the patient within 3 weeks after the infusion of secretin.

Table I

Symptoms Before Secretin Infusion	Progress within 3 Weeks After the Secretin Infusion
Two words	100's of words - will repeat approximation of any word requested.
No sentences	Short sentences - such as; "I love you", "I want juice", "Good night mommy", "Thank you, daddy".
No flash cards	40 - 50 flash cards.
No focus on requested tasks	Will sit and watch carefully. Will perform most tasks after watching once or twice. For instance, will sort by color or category. Will construct more complicated puzzles. Will respond appropriately to questions.
Diapers only	Completely potty trained.
Watch Videos	Now, gets "involved" interactively with his videos. He will imitate the hand motions, sing the songs or dance to the music.
Consistent sleeping problems. Although these were much worse when he was 18-24 months, prior to the procedure he was still up numerous times each night.	Has slept through almost every night entirely.
Infrequent (1-2 times/week) "spinning" episodes.	No spinning episodes.
Abnormal bowel movements.	Normal bowel movements.
Excessive water consumption approximately 50 cups per day.	Excessive water consumption - no change approximately 50 cups per day.

Table I (continued)

Symptoms Before Secretin Infusion	Progress within 3 Weeks After the Secretin Infusion
Limited Diet Preferences (French Toast, bananas, French Fries, pancakes, crackers, cookies, raisins, chocolate, chicken nuggets).	No Change.
No apparent connections made between language and objects.	Many connections made between new language learned and objects. Recites names he has learned on flash cards when he sees the same on computer game or video.
No response to request for gestures.	Responds to all kinds of thins such as, "blow a kiss", "Wave bye bye", "Say bye bye", etc. Will often now spontaneously say these things himself.
No interest in drawing.	Wants to draw constantly. Will draw complete face and name the parts as he draws.
Did not imitate commands.	Will imitate almost any multi-step command.
Minimal eye contact.	Eye contact 75% of the time.

Biomedical changes were also measured in the patient. A SPECT scan of the patient indicated that the perfusion of the right posterior parietal and right temporal lobes was improved. Blood tests taken after the treatment also indicated a rise in serotonin levels, and the patients rubella titers dropped from 5.8 to 2.3.

Although the behavioral improvements continued, the rate of the patient's progress appeared to decrease at about 5 weeks. At the request of the patient's parents, a second infusion of secretin was performed about 9 months after the first infusion, and a third infusion of secretin was performed about three months after the second infusion. The second and third infusions of secretin achieved the same results in the patient.

EXAMPLE 2

At the time of this treatment, the patient was about 4 years old. Secretin was administered transdermally using pharmaceutical grade dimethyl sulfoxide (DMSO) (generally 99.9% pure) available from Clinic Service Co., Box 2512, Hemet CA 92543. The secretin (Secretin-Ferring) was administered daily in a dosage of about 75 CU over a five day period (i.e., about 15 CU daily). For each treatment, about 4 drops of DMSO were placed onto the skin of the patient, about 15 CU of the crystalline secretin was placed onto the DMSO, and the composition was rubbed into the skin.

The administration of secretin transdermally on a daily basis in this way has resulted in even more dramatic and significant improvements in the patient. Within a period of about 6 months, the patient has progressed to spontaneous and conversational language. When the daily dose of secretin is stopped, the autistic behavioral symptoms return.

It is important to note that similar results have been seen in numerous other autistic children using an intravenous administration of secretin in accordance with the teachings of the present invention, in order to validate the findings of the present invention.

Although the present invention is not limited by theory, it is believed that some autistic spectrum disorders are caused by a secretin deficiency resulting in a dysfunction of the pancreas. One function of the hormone secretin is to stimulate the pancreas to release bicarbonate and water, which change the pH in the gut from acid to alkaline, thereby facilitating the action of digestive enzymes. The gastrointestinal disorders, such as an inability to digest gluten and casein, in autistic

patients is possibly caused by this failure of the pancreas to release enzymes.

One possibility is that abnormal opioid peptides in the gut create problems in the brain. These abnormal opioid peptides have been found to diminish on a casein free and gluten free diet.

The gastric inflammation observed in the patient in the above EXAMPLE 1 suggests that the improper pH resulting from this dysfunction of the pancreas may be a cause of the digestive problems and malabsorption of essential minerals and nutrients found in many individuals with autism. The unusual secretion by the pancreas in response to the secretin, as observed in EXAMPLE 1, further suggests that this dysfunction of the pancreas is caused by a secretin deficiency.

In addition to this effect on the digestive function, secretin also appears to improve the abnormal brain activity in individuals having symptoms of autism. The increased blood flow in the brain detected during a SPECT scan after administering secretin in EXAMPLE 1 supports this theory. While causing pancreatic secretions, secretin also stimulates the production of cholecystokinin (CCK). Deficiencies in CCK have been linked to other neurological disorders, such as schizophrenia, and CCK production has been found to be related to levels of the neurotransmitter serotonin. Thus, secretin may be indirectly related to the body's natural production of serotonin. The increase in serotonin levels in the blood after the procedure in EXAMPLE 1 supports this relationship between secretin and serotonin.

Without proper modulation of neurotransmitter levels (i.e., serotonin) in the brain, the brain will not function properly. The inability to modulate neurotransmitter levels has been found to be related to

other neurological conditions as well as autism. Thus, a secretin deficiency may cause an imbalance or improper modulation of neurotransmitter levels that results in autistic spectrum disorder or other neurological disorders. Administering secretin to patients with these disorders will modulate the neurotransmitter levels and correct the behavioral symptoms, such as the inability to process language and other maladaptive behavioral patterns. The secretin may also correct abnormalities in immune system functions, as indicated by the reduction of measles, mumps and rubella antibodies in the patient after the secretin administration in EXAMPLE 1.

Secretin has also been found to stimulate dopamine production through its precursor, tyrosine hydroxylase. Dopamine levels have been implicated in a variety of mental and behavioral disorders such as Parkinson's and Alzheimer's disease.

A secretin deficiency can therefore account for the gastrointestinal disorders as well as the behavioral symptoms found in many individuals with autistic spectrum disorder.

The therapeutic possibilities of the use of secretin appear to have been overlooked in the medical literature. For example, Guyton and Hall, in their widely used Textbook of Medical Physiology (9th edition, 1995-1997) mention briefly in passing that secretin can increase cellular utilization of insulin. Recent research suggests that insulin is required for normal brain functioning. (See also Science, vol. 280, April 24, 1998, p. 517-518). Furthermore, immunological disorders related to abnormally high levels of measles, mumps, and rubella (MMR) titers may also be treatable with secretin. Additionally, secretin is believed to stimulate antibodies to cows milk protein (and perhaps other proteins). Autism and other PDD's may be connected to

protein intolerance and secretin may increase the body's tolerance to such protein(s). Secretin may also have histamine blocking capabilities.

Although the above examples use Secretin-Ferring, the present invention contemplates other forms of natural or synthetic (or recombinant) secretin, e.g., porcine or human. The present invention also contemplates using other types of transdermal carrier substances in addition to DMSO. Further, the present invention contemplates alternative ways of administering secretin including, but not limited to, administering secretin transdermally with a gel (such as Pluronic-Lecithin-Organogel (PLO gel, from Gallipot, Inc., St. Paul, MN) made of Pluronic® F127NF and a 1:1 mixture of soy lecithin:isopropyl palmitate, kept at a pH of 5 with a buffer, e.g., potassium sorbate), lotion or patch; administering secretin with a suppository; administrating secretin orally, as tablet, capsule or lozenge; administrating secretin by inhalation (e.g., as an aerosol) either through the mouth or the nose; and administering secretin intranasally (e.g., as a snuff). Such alternative methods of administering secretin are less invasive, do not have to be carried out by a doctor at a medical facility, and are less expensive. In addition, the level or dose of administration of secretin can be varied from those examples stated herein including, for example, intravenous administration over a period of time of several hours instead of several minutes and/or a smaller, maintenance or daily dose administered intramuscularly, transdermally or by other methods as disclosed herein or their equivalent.

A further alternative method of transdermally administering secretin includes the use of acoustic waves to permeate the skin. For example, acoustic waves generated using ultrasound or a shockwave from a pulsed

laser have been found to make the skin temporarily permeable. A few minutes of low-frequency ultrasound (sound greater in frequency than 20 kilohertz) creates tiny cavities through which the secretin (alone or combined with another transdermal carrier substance) can be diffused.

Accordingly, the methods of treating autism by administering secretin and/or causing the body to naturally secrete required amounts of secretin corrects the secretin deficiency, improving the digestive functions in autistic patients previously experiencing intestinal difficulties and improving communication, cognition, and socialization capabilities of autistic patients. Since other neurological disorders, such as depression, obsessive-compulsive disorder, Alzheimer's, allergies, anorexia, bulimia, schizophrenia, also involve abnormal modulation of neurotransmitter levels, these disorders can also be treatable with secretin and/or the stimulation of pancreatic juices. Further, other disorders related to serotonin and dopamine may also be treatable with secretin.

Modifications and substitutions by one of ordinary skill in the art are considered to be within the scope of the present invention which is not to be limited except by the claims which follow.

What is claimed is:

1. A method for treating an individual exhibiting a symptom of a neurological or immunological disorder, the method comprising administering to the individual an amount of secretin effective to improve one or more symptoms of the disorder.

2. The method of claim 1, wherein the neurological or immunological disorder is selected from the group consisting of depression, obsessive-compulsive disorder, Alzheimer's, allergies, anorexia, bulimia, schizophrenia, Attention Deficit Disorder (ADD), and Attention Deficit Hyperactivity Disorder (ADHD).

3. The method of claim 1, wherein the effective amount of secretin is administered by infusion.

4. The method of claim 3, wherein administering the effective amount of secretin by infusion includes the step of intravenously infusing secretin in an amount of about 2 clinical units (CU) per kilogram (kg) of body weight.

5. The method of claim 1, wherein the effective amount of secretin is administered transdermally.

6. The method of claim 5, wherein administering the effective amount of secretin transdermally includes:

applying a transdermal carrier substance to a portion of the skin of the individual; and

applying crystalline secretin in the effective amount onto the transdermal carrier substance.

7. The method of claim 6, wherein the transdermal carrier substance comprises dimethyl sulfoxide (DMSO).

8. The method of claim 5, wherein the effective amount of secretin includes between 5 and 20 clinical units (CU) of crystalline secretin per dose.

9. The method of clam 5, wherein administering secretin transdermally includes administering the effective amount of secretin with a patch to be applied to a portion of the skin of the individual.

10. The method of claim 5, wherein administering secretin transdermally includes administering the effective amount of secretin using acoustic waves causing the secretin to permeate a skin surface of the individual.

11. The method of claim 1, wherein the effective amount of secretin is administered orally.

12. The method of claim 11, wherein the effective amount of secretin is administered orally using an oral carrier selected from the group consisting of a tablet, capsule, or lozenge.

13. The method of claim 1, wherein the effective amount of secretin is administered using a suppository.

14. The method of claim 1, wherein the effective amount of secretin is administered by inhalation or intranasally.

15. The method of claim 1, wherein the effective amount of secretin includes an amount of secretin sufficient to increase serotonin levels in the brain of the individual.

16. Secretin for use in treating a neurological or immunological disorder.

17. The use of secretin for the manufacture of a medicament for the treatment of a neurological or immunological disorder.

18. A composition for treatment of a neurological or immunological disorder in an individual comprising an

effective amount of secretin and a physiologically acceptable carrier.

19. The composition of claim 18, wherein the physiologically acceptable carrier includes a transdermal carrier substance.

20. The composition of claim 19, wherein the transdermal carrier substance comprises dimethyl sulfoxide (DMSO) or Pluronic-Lecithin-Organogel (PLO).

21. The composition of claim 18, wherein the effective amount of secretin comprises about 15 clinical units (CU) of crystalline secretin per dose.

22. The composition of claim 18, wherein the effective amount of secretin comprises about 2 clinical units (CU) per kilogram (kg) of body weight of an individual per dose.

23. The composition of claim 18, wherein the physiologically acceptable carrier comprises an oral carrier.

24. The composition of claim 18, wherein the physiologically acceptable carrier comprises an inhalable carrier.

25. A method for treating an individual exhibiting symptoms of autism, the method comprising transdermally administering to the individual an amount of secretin effective to improve one or more criteria for autistic disorder.

26. The method of claim 25, wherein administering the effective amount of secretin transdermally includes the steps of:

applying a transdermal carrier substance to a priority of the skin of the individual; and

applying crystalline secretin in the effective amount onto the transdermal carrier substance.

27. The method of claim 25, wherein the transdermal carrier substance comprises dimethyl sulfoxide (DMSO).

28. The method of claim 25, wherein the effective amount of secretin includes about 15 clinical units (CU) of crystalline secretin per dose.

29. Secretin for use in treating symptoms of autism by transdermal administration.

30. The use of secretin for the manufacture of a medicament for the treatment of symptoms of autism by transdermal administration.

31. A method for treating an individual exhibiting a symptom of a neurological or immunological disorder, the method comprising stimulating secretion of pancreatic juices in the individual.

32. The method of claim 31, wherein secretion of pancreatic juices is stimulated by administering to the individual an amount of secretin effective to improve one or more symptoms of the disorder.

33. The method of claim 31, wherein the secretin is administered by infusion.

34. The method of claim 31, wherein the secretin is administered transdermally.

35. The method of claim 31, wherein stimulating secretion of pancreatic juices increases a level in the individual of at least one of serotonin, dopamine, and CCK.

36. The method of claim 31, wherein stimulating secretion of pancreatic juices induces secretion of an

amount of secretin in the individual effective to improve one or more symptoms of the disorder.

37. The method of claim 36, wherein secretion of secretin is induced by stimulating the duodenum of the individual.

38. The method of claim 31, wherein the disorder is autism.

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(72) Inventors: BECK, Victoria; 11 McIntosh Lane, Bedford, NH 03110 (US). RIMLAND, Bernard; 4758 Edgeware Road, San Diego, CA 92116 (US).

(74) Agent: FASSE, J., Peter; Fish & Richardson, P.C., 225 Franklin Street, Boston, MA 02110–2804 (US).

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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 833 722 A (GRAYBILL D) 3 September 1974 (1974-09-03) the whole document ---	1-24, 31-37
X,P	WO 98 52593 A (UNIV MARYLAND BALTIMORE) 26 November 1998 (1998-11-26) the whole document ---	1-38
X,P	PERRY R (REPRINT) ET AL: "Secretin in autism" JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY, VOL. 8, NO. 4, PP. 247-248. , XP000857737 the whole document ---	1-38
X	WO 94 16756 A (MIRIS MEDICAL CORP) 4 August 1994 (1994-08-04) claims 1,16; table 2 --- -/--	16,18, 24,29

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 December 1999	29/12/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fernandez y Branas,F

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/13061

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate. of the relevant passages	Relevant to claim No.
X	US 4 462 991 A (HIGUCHI TAKERU ET AL) 31 July 1984 (1984-07-31) the whole document	16,18, 23,29
X	RENE THOMAS FOLSE: "Secretin Therapy" THE CHILD PSYCHOLOGIST, 'Online! XP002125947 Retrieved from the Internet: <URL:http//www.childpsychology.com/autism/ secretin.htm> 'retrieved on 1999-12-16! the whole document & JOURNAL OF THE ASSOCIATION FOR ACADEMIC MINORITY PHYSICIANS, 1998 9(1): 9-15	1-4, 16-18, 22,25, 28, 31-33, 35-38
X	KEVIN MCSHANE: "Secretin in autism" AUTISM SOCIETY OF ALABAMA, 'Online! XP002125948 Retrieved from the Internet: <URL:http://www.autism-alabama.org/secreti n2.htm> 'retrieved on 1999-12-16! the whole document & JOURNAL OF THE ASSOCIATION FOR ACADEMIC MINORITY PHYSICIANS 1998 9(1): 9-15	1-4, 16-18, 22,25, 28, 31-33, 35-38
A	WO 96 06636 A (CRANDALL WILSON TRAFTON) 7 March 1996 (1996-03-07) page 6 -page 9	19-21
A	WILLIMANN H ET AL: "LECITHIN ORGANOGEL AS MATRIX FOR TRANSDERMAL TRANSPORT OF DRUGS" JOURNAL OF PHARMACEUTICAL SCIENCES,US,AMERICAN PHARMACEUTICAL ASSOCIATION. WASHINGTON, vol. 81, no. 19, page 871-874 XP000371811 ISSN: 0022-3549 the whole document	19-21

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/ 13061

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 1-15, 25-28, 31-38 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [X] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/ US 99/13061

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-24, 25-30, 31-37, 38

   Claims 1-24 (partially), 25-30 (completely), 31-37 (partially) and 38 (completely) in so far methods, uses and compositions of secretin for treating neurological disorders; idem for treating autism

2. Claims: 1-24, 31-37

   Claims 1-24 (partially) and 31-37 (partially) in so far methods, uses and compositions of secretin for treating immunological disorders

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 99/13061

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3833722 A	03-09-1974	NONE	
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